IJBPAS, March, 2023, 12(3): 1147-1157

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

ROLE OF CRIZANLIZUMAB FOR SICKLE RED CELLS DISEASE

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Received 14th April 2022; Revised 11th May 2022; Accepted 1st Aug. 2022; Available online 1st March 2023

https://doi.org/10.31032/IJBPAS/2023/12.3.6946

ABSTRACT

Sickle cell disease (SCD) is an inherited monogenic disease characterized by distorted red blood cells that causes vaso-occlusion and vasculopathy. These red cells can damage the vessel wall and activate P-selectine which can cause the vessel wall stick to other blood constitute and form cluster. These clusters in the blood stream can create the blockage and obstruct the flow of blood and oxygen in the tissues. Crizanlizumab is a humanized monoclonal antibody binds to P-selectine and blocks the interaction of endothelium and blood constituents. It's infusion into the vein reduce the adhesion of blood vessel and cells and prevent from vaso-occlusion crises. In this present model bio-physical properties of distorted red blood cells studied in sickle cell disease. In steady-state, at very low Reynolds number (inertial effect neglected) lubrication theory has been implemented to study the effect of deformation parameter and compliance of the red blood cells in the blood flow due to adhesion. The governing equations have been solved for suitable boundary and matching conditions. The results have been shown graphically and agree semi quantitatively with experimental results. Sickle RBCs are highly viscous liquid filled membranes, In the microcirculation after releasing the oxygen to tissue Hb-SS turn into more rigid red blood cells, leads to decrease cell velocity as compared to the healthy red blood cell. Slip effect has been discussed in the reference of adhesion for blockage in the blood stream in more viscous region due to diseased state. Results also verify that plasma in the capillary on the average moves slower than the cells. It is concluded that rheological and bio-mechanical properties of

the sickle RBCs and sickle blood plays an essential role in better understanding of the pathophysiology of the disease.

Keywords: Pathophysiology, Vaso-oclusive, Crizanlizumab, Sickle cell disease, Reynolds number

INTRODUCTION

Sickle cell anemia is one of a group of disorders known as sickle cell disease. Sickle cell anemia is an inherited red blood cell disorder in which there aren't enough healthy red blood cells to carry oxygen throughout your body. Normally, the flexible, round red blood cells move easily through blood vessels. In sickle cell anemia, the red blood cells are shaped like sickles or crescent moons. These rigid, sticky cells can get stuck in small blood vessels, which can slow or block blood flow and oxygen to parts of the body. Blood is a multiphase fluid, primarily made up of red blood cells (RBCs), white blood cells (WBCs) and platelets suspended in plasma. Oxygenated blood flows away from the heart to different organs through systemic circulation. Healthy RBCs are biconcave disc with a mean diameter of 6-8μ and a maximal thickness of 2 μ. They represent approximately 40 to 45% by volume of the average human blood and more than 99% of the blood cells. RBCs are highly deformable cells, which can easily squeeze through the capillaries (where internal diameter less than of their own) and transport oxygen and nutrients to the different part of the body through network of vessels **(Figure 1)**. Crizanlizumab is a humanized IgG2 monoclonal antibody used to reduce the frequency of vaso-occlusive crises in patients with sickle cell disease. Sickle cell disease is a genetically inherited condition prevalent in the Middle East, Africa, and certain parts of India. The genetic mutation associated with this disease leads to the formation of abnormal, sickle shaped red blood cells that aggregate and block blood vessels throughout the body, causing vaso-occlusive crises. Sickle cell disease can lead to excruciating pain, stroke, infection, and various other complications arising from the blockage of blood vessels. In 1962, first time Thomas **[22]** reported a large number of thin, elongated, sickle-shaped cells in blood smear of an African. After that Wang and Skalak **[23]** have advocated that the existence of a molecular disease because of defective hemoglobin molecule (HbS) named as sickle cell disease (SCD). This is first identified molecular disease inherited genetically. The genetic basis of SCD is the substitution of valine for glutamic acid in the sixth position of each β globin chain of the hemoglobin protein $\beta^6: Glu \rightarrow Val$ **[17-20]**.

Within the microcirculation deoxygenated hemoglobin HbS molecules alter their configuration and polymerization occurs, which generates rigid fibers of HbS that injure the membrane and cytoskeleton of the RBC and consequent change in biomechanical and rheological properties **[11-16]**. Morbidity and mortality due to vaso-occlusion event in SCD under clinical manifestation encompass recurrent painful crises, bone marrow infraction, organ damage and stroke. Blood viscosity of sickle cell patient's is remarkably high under oxygenated condition results in reduced RBC deformability **[7, 21, 24, 25]** and higher plasma viscosity results higher protein concentration by which RBC aggregation (rouleaux formation) **[2-6]** occur. Early viscometric studies reveals that sickle blood cells are more viscous and less deformable than healthy red blood cells **[1, 8, 9, 10]**.

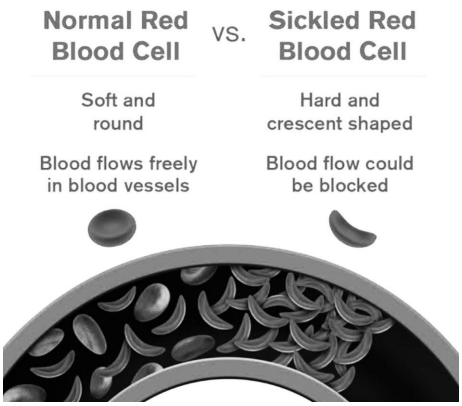

Figure 1: Normal Red Blood Cell vs. Sickled Red Blood Cell

In this paper, we focused on the flow in the capillary for axisymmetric cell-deformation and investigated the flow profile in healthy and sickle blood. To describe the capillary flow, we have assumed the flow of plasma trapped between successive erythrocytes (treated plasma as a continuum media where the continuum mechanics laws are applied). Equations of motion are given by Navier-Stokes equations and continuity equation (due to incompressibility) for the fluid. The capillary has treated as a cylindrical duct, symmetrical about the axis and single file flow of the red blood cells have considered. Taking the height of lubricating film between pellet and tube wall by Higgins *et al*., **[6]** formed by the effect of cell and tube compliances as well as pressure difference in the capillary flow. In steady-state at very low Reynolds number lubrication theory has been implemented and neglected inertial effects. Since plasma in the capillary on the average moves slower than the cells hence

we have investigated the effect of motion of highly viscous liquid filled membrane in narrow tube and developed the model of capillary flow and occurrence of vaso occlusion.

Mathematical Formulation of the problem

A mathematical model has been introduced for two dimensional cartesian geometry of the cell in capillary **(Figure 2)**. The cell is similar in size to the capillary diameter and deforms in compliance of the fluid stresses. The red cell is modelled as containing incompressible fluid inside, deform axis-symmetrically, in single file flow rub alongside the endothelial wall and cell to cell interactions are neglected **[9]**. Frame of reference with the flow of plasma (exterior to red blood cell)

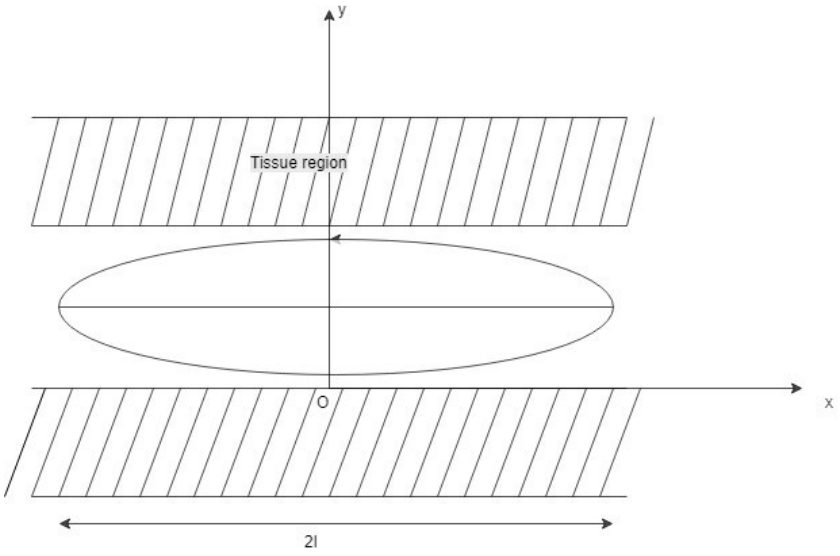

Figure 2: Diagram for single file flow of red cell blood cell in the capillary

Governing Equations

The governing equations for the motion of the plasma are given by Navier-Stokes equations and the continuity equation **[18]**.

Navier-Stokes equation for motion at some point in the fluid may written as:

$$\frac{Du'}{Dt} = -\frac{1}{\rho}\nabla P' + \frac{\mu}{\rho}\nabla^2 u' \qquad (1)$$

Where P' is Pressure, μ is shear viscosity of the plasma, u' is axial velocity of the plasma relative to the red blood cell, ρ is density of blood, ∇ is gradient operator.

Equation of continuity:

$$\frac{\partial u'}{\partial x'} + \frac{\partial v'}{\partial y'} = 0 \qquad (2)$$

Where (x, y) are cartesian co-ordinate of any point in the capillary, x, y axes are taken as along and across the capillary, u' and v' are the velocities in these

directions. Since motion is under following assumption:

Plasma must have swirling "bolus-flow" motion and lubrication theory is used to describe the squeezing flow of plasma in between the cell and the tissue wall **[7]**. Thickness of the fluid layer between the cell and the wall is sufficiently small so that by lubrication theory, Stoke's equations can be reduced in to the Reynolds's equation **[10]**.

Hence equations of motion can be written as:

$$\frac{\partial P'}{\partial y'} = 0 \qquad (3)$$

According to the **[22]** fluid film thickness h' of the plasma between the cell and the tissue wall is represented as:

$$-\frac{\partial P'}{\partial x'} + \mu \frac{\partial^2 u'}{\partial y'^2} = 0 \qquad (4)$$

$$h' = (\alpha + \beta)(P' - P'_0) + \frac{x'^2}{4a} \qquad (5)$$

Where P' is the local pressure in the fluid film region, P_0' is reference pressure, a is focal length of initially assumed shape of parabola which is related to curvature $k$of the pellet at it's point of maximum diameter. x is measured axially downstream from the point where the cell(pellet) cross- section has its maximum radius, α and $\beta$are radial compliances of tube and the cell which are not separately significant, but appears only in linear combination $\alpha + \beta$. So that $(\alpha + \beta)(P' - P_0')$ represent the further deformation due to increased pressure in lubricating film between cell and the inner tube wall **[21]**. Here U_0 and V_0 are the reference velocities of cell and plasma, when cell is being forced along the tube because of pressure difference at velocity U_0 used to non-dimensionalize the system of equation to find the solution of the above equation of motion **[6]**. It is convenient to take the dynamics of the lubricating film is nearly same as the cell velocity.

The above assumption applied in two different cases.

Governing equations and fluid film thickness are given above in equations (3)(4) and (5)

$$\frac{\partial P}{\partial y} = 0$$

$$\frac{\partial P}{\partial x} = \mathrm{Re}\frac{\partial^2 u}{\partial y^2}$$

Dimensionless fluid film thickness

$$h = \alpha'\left(\frac{P}{P_0} - 1\right) + \xi x^2 \qquad (6)$$

where

Deformation parameter $e = \frac{l^2}{4aH}$

Radial compliance of the cell $b = \frac{(\alpha+\beta)'\rho {V_0}^2 P_0}{H}$

Boundary and matching condition in Dimensionless form:

$$\left.\begin{array}{lll} u = \frac{U_0}{V_0} & at & y = h \\ u = -n\frac{\partial u}{\partial y} & at & y = 0 \\ v = 0 & at & y = h \end{array}\right\} \quad (7)$$

Here

$'n'$ is slip parameter

Solution of the problem:

Equation of motion have been solved by using above boundary conditions, we get the solution for axial velocity as given below:

$$u = R_e \frac{dP}{dx}\left[y^2 - h^2\left[\frac{y-n}{h-n}\right]\right] + \frac{U_0}{V_0}\left[\frac{y-n}{h-n}\right] \quad (8)$$

RESULTS AND DISCUSSION

The model shown before contributing to the fact that height of the fluid film between the cell and capillary wall depends on the deformation of cell, local pressure and linear combination of radial compliance of cell and tube. Leak back action (net flux backwards per unit length) continues the capillary flow. The results obtained in the study consist of the expressions for the axial velocity component of the fluid flow in a capillary for the flow of plasma with the cell in eq. (8).

Figures (3) and (5) show the variation of thickness of lubricating film between the cell and capillary wall with deformation parameter and compliance of the cell (in SCD, cell compliance participates more as compare to tube). **Figure (3)** shows that the height of lubricating film between the cell and capillary wall increases with axial distance in the direction of capillary length and rises with small increase of deformation parameter (less deformation shows less height of plasma in the capillary) which is similar as **[21]**.

Figure (4) shows that variation in axial velocity component of flow in a capillary with axial distance for different slip parameter. It shows that axial velocity component increases with axial distance and decreases with increases in slip parameter. Slip parameter affects the motion negatively it means that increase in slip parameter opposes the motion of fluid in capillary, i.e. shows resistance in the motion of fluid. It is clear that increase in flow resistance shows low velocity this result is similar to the findings of **[1]**. In the case of sickle RBC this result supported by **[15]** as they are more adherent to endothelial cell than healthy RBCs, which increases resistance in motion during microcirculation.

Figure (5) represents that the variation of axial velocity component for different deformation parameter at slip parameter .09 and .05. They are at increasing pressure drop. It is clear from the graph that increases in deformability (deformation parameter) shows increase in axial velocity component.

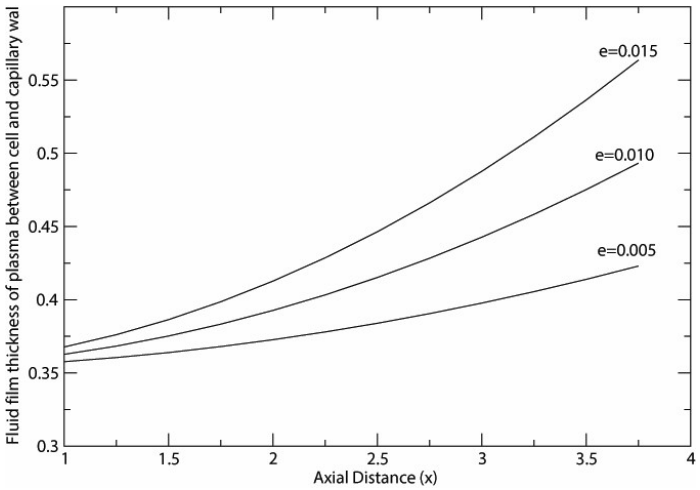

Figure 3: Variation of plasma film thickness (h) with axial distance for different values of deformation parameter (e) in capillary

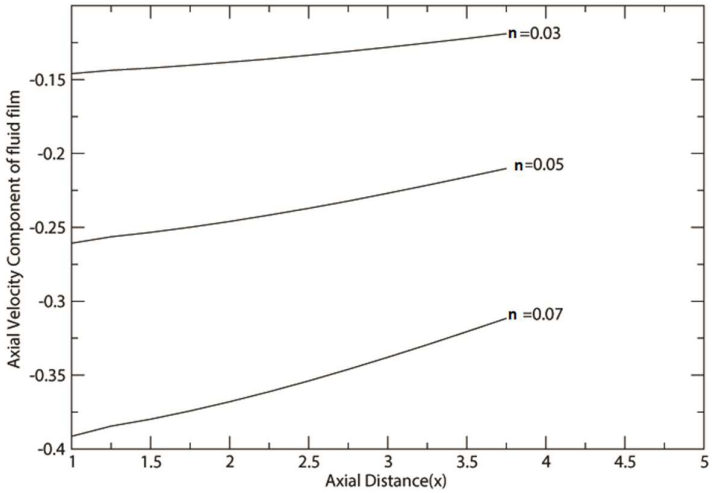

Figure 4: Variation of Axial velocity component (u) with axial distance (x) for different slip parameter (n)

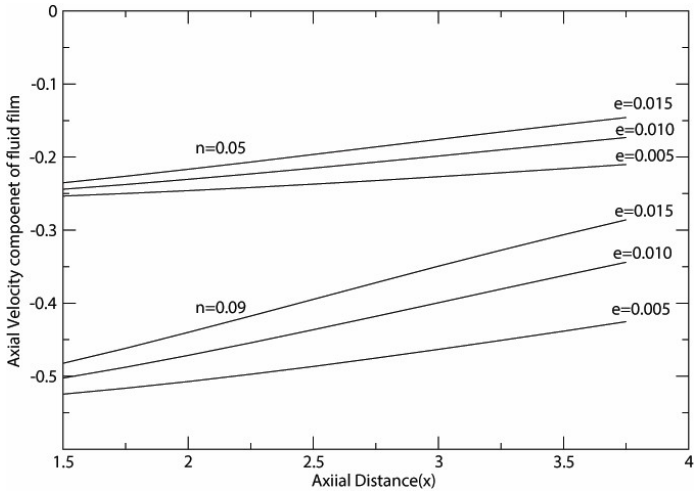

Figure 5: Variation of axial velocity component (u) for different slip parameter (n) with axial distance (x) at different deformation parameter (e)

It is also clear from the graph that variation in axial velocity component varies with varying slip parameter that is increase in slip parameter shows decrease in velocity and the similar pattern for deformability. The above result follow the same trend as [14, 13] as decreased erythrocytes deformability results in slower movement through the capillaries.

CONCLUSION:

Sickle blood is known to undergo rheological and mechanical changes if the oxygen level falls low enough. In SCD, due to abnormal polymerization of hemoglobin erythrocytes become comparatively hard and adhesive. These damaged red cells make blood vessels inflamed and irritated the vessel wall and activate P-selectine which can cause the vessel wall stick to other blood constitute and form cluster. These clusters in the blood stream can create the blockage and obstruct the flow of blood and oxygen in the tissues. Crizanlizumab is a humanized monoclonal antibody binds to P-selectine and blocks the interaction of endothelium and blood constituents. It works by making the red blood cells and vessel less adhesive.

The model predicts that the height of the lubricating film between the cell and capillary wall affects the flow of blood in the capillary in diseased condition. It is also clear from the results that change in the deformation parameter and red cell compliance proposed an effective variation in the plasma film thickness, which obstruct the continuous movement of RBCs during micro-circulation. However, sickle RBCs are comparatively less compliant and have weak deformation tendency after deoxygenation. Smaller width gap (width of lubricating film) between the cell and capillary wall shows less fluid leak back (net flux backwards per unit length) and opposes the flow of blood in capillary cause vaso-occlusion. Crizanlizumab is given as an infusion into a vein to reduce the frequency of vaso-oclusive crises and it works by making the red blood cells and vessel wall less adhessive. Hence Crizanlizumab reduces stickness of the red blood cells and other constituent with withvessel wall and promote the flow and prevent from vaso-occlusion and it works by making the red blood cells less adhessivness.

Acknowledgments: The authors would like to thank to the Department of Science and Technology (DST), INDIA for supporting this research under WOS-A Scheme (Project ID: SR/WOA-A/PM-94/2017).

REFERENCES

[1] Bali R., Mishra S., Dubey S., (2008),"A mathematical model for red cell motion in narrow capillary surrounded by tissue", Applied Mathematics and Computation,

196(1):193-199. https://doi.org/10.1016/j.amc.2007.05.065.

[2] Bali, R., Mishra, S., Mishra, M., (2011), "Effect of deformation of red cell on nutritional transport in capillary-tissue exchange system" Applied Mathematics, 2(11):1417. https://www.scirp.org/pdf/AM20111100017_67327786.pdf.

[3] Ballas, S. K., Mohandas, N., (2004), "Sickle red cell microrheology sickle blood rheology"Micro-circulation,11(2):9-25. https://doi.org/10.1080/10739680490279410.

[4] Frenette. P. S., (2002), "Sickle cell vaso-occlusion: multistep and multicellular paradigm", Current Opinion in Hematology, 9(2):101-106. DOI:10.1097/00062752-200203000-00003.

[5] Herrick, J. B., (2001), "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia", The Yale Journal of Biology and Medicine, 74(3):179. DOI: 10.1001/jama.2014.11011.

[6] Higgins, J. M., Eddington, D. T., Bhatia, S. N. Mahadevan, L., (2007), "Sickle cell vaso-occlusion and rescue in a microfluidic device", Proceedings of the National Academy of Sciences, 104(51):20496-20500. DOI: 10.1073/pnas.0707122105.

[7] Klug, P. P., Lessin, L. S., Radice. P., (1974), "Rheological aspects of sickle cell disease", Archives of Internal Medicine, 133(4):577-590. https://doi.org/10.1001/ARCHINTE.1974.00320160071007

[8] Lighthill, M. J., (1968), "Pressure-forcing of tightly ting pellets along uidlled elastic tubes", Journal of Fluid Mechanics, 34(1):113-143. https://doi.org/10.1017/S0022112068001795

[9] Liu, Y., Zhang, L. Wang, X., Liu, W. K., (2004), "Coupling of navier stokes equations with protein molecular dynamics and its application to hemodynamics". International Journal for Numerical Methods in Fluids, 46(12):1237-1252. https://doi.org/10.1002/fld.798

[10] Lomen, D. O., Gross, J. F., (1977), "A mathematical model of the effect of oxygen consumption on the resistance to flow of sickle cell blood in capillaries", Mathematical Biosciences, 37(1-2):63-79. https://doi.org/10.1016/0025-5564(77)

[11] Mohandas, N., Evans, E., (1984), "Adherence of sickle erythrocytes to vascular endothelial cells: requirement for both cell membrane changes and plasma factors", Blood, 64(1):282-287. https://doi.org/10.1182/blood.V64.1.282.282

[12] Natarajan, M., Udden, M. M., McIntire, (1996), "Adhesion of sickle red blood cells and damage to interleukin-1 beta stimulated endothelial cells under ow in vitro", Blood, 87(11):4845-4852. https://pubmed.ncbi.nlm.nih.gov/8639858/

[13] Pauling, L., Itano, H. A., Singer, S. J., Wells, I. C., (1949), "Sickle cell anemia, a molecular disease", Science, 110(2865):543-548. https://doi.org/10.1126/science.110.2865.543

[14] Pedrizzetti. G., (1998), "Fluid ow in a tube with an elastic membrane insertion", Journal of Fluid Mechanics, 375:39-64. http://dx.doi.org/10.1017/S0022112098002316

[15] Secomb, T. W., (1987), "Flow-dependent rheological properties of blood in capillaries", Microvascular Research, 34(1):46-58. https://doi.org/10.1016/0026-2862(87)90078-1

[16] Secomb, T. W., (1991), "Red blood cell mechanics and capillary blood rheology" Cell Biophysics, 18(3):231. https://doi.org/10.1007/bf02989816

[17] Secomb, T. W., (2017), "Blood ow in the microcirculation", Annual Review of Fluid Mechanics, 49:443-461. https://doi.org/10.1146/annurev-fluid-010816-060302

[18] Secomb, T. W., Hsu, R., Pries, A. R., (2001), "Motion of red blood cells in a capillary with an endothelial surface layer: Effect of low velocity", American Journal of Physiology-Heart and Circulatory Physiology, 281(2):H629-H636. https://doi.org/10.1152/ajpheart.2001.281.2.h629

[19] Secomb, T. W., Skalak, R., Ozkaya, N., Gross, J. F., (1986), "Flow of axisymmetric red blood cells in narrow capillaries", Journal of Fluid Mechanics, 163:405-423. https://doi.org/10.1017/S0022112086002355

[20] Sorette, M. P., Lavenant, M. G., Clark, M. R., (1987), "Ektacytometric measurement of sickle cell deformability as a

continuous function of oxygen tension Blood", 69(1):316-323.https://pubmed.ncbi.nlm.nih.gov/3790727/

[21] Stuart, J., Nash, G. B., (1990), "Red cell deformability and haematological disorders", Blood Reviews, 4(3):141-147. https://doi.org/10.1016/0268-960X(90)90041-P

[22] Thomas, H. W., (1962), "The wall effect in capillary instruments: an improved analysis suitable for application to blood and other particulate suspensions", Biorheology, 1(1): 41-56. 10.3233/ BIR-1962-1106

[23] Wang, H., Skalak, R., (1969), "Viscous ow in a cylindrical tube containing a line of spherical particles", Journal of Fluid Mechanics, 38(1):75-96. https://doi.org/10.1017/S00221120 6900005X

[24] Ye, T., Shi, H., Peng, L., Li,Y., (2017), "Numerical studies of a red blood cell in rectangular microchannels", Journal of Applied Physics, 122(8):084701. https://doi.org/10.1063/1.5000357

[25] Zarda, P. R., Chien, S., Skalak, R., (1977), "Elastic deformations of red blood cells", Journal of Biomechanics,10(4):211-221. https://doi.org/10.1016/0021-9290(77)90044-6.